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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
CHERNYSHEV, OLGA N

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/26/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/826,290	DURHAM ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-71* is/are pending in the application.

4a) Of the above claim(s) *56-58 and 68-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-55 and 59-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the claims

1. Claims 1-50 have been cancelled and claims 51-71 have been added, as requested in the amendment of Paper No. 14, filed on August 27, 2002. Claims 51-71 are pending in the instant application.

Election/Restrictions

2. Applicant's election with traverse of claims 4-10, drawn to a method for screening for Alzheimer's disease by detecting API-6 in Paper No. 14 is acknowledged. The traversal is on the ground(s) that "API-3, API-6, API-47, API-58, API-145, and API-239 are all fragments of a single protein molecule identified by Accession Number O15179 [...]. Accordingly, these APIs require a single search, and thus should be treated as a single invention for examination purposes" (page 5, last paragraph of Response). This is not found persuasive because according to Table IV on pages 25-26 of the instant specification API-6 is represented by four amino acid sequences, SEQ ID NOs: 36-39. These sequences do not share a common structural feature and a separate search is required for each amino acid sequence. Further, the total number of sequences recited within "API-3, API-6, API-47, API-58, API-145, and API-239" exceeds thirteen (the number of sequences corresponding to API 151 is not known because such information is not present in Table IV), which goes greatly above the number of sequences permitted for a single unburdensome search in a single application.

The requirement is still deemed proper and is therefore made FINAL.

Newly submitted claims 56 and 57 are directed to an invention corresponding to originally presented and non-elected Groups I to CXCI; claims 68-71 are directed to an invention originally presented and non-elected Groups CDXL to DCLXXXVII (see section 3 of Paper No. 10). Further, claim 58 recites non-elected API-145.

Accordingly, claims 56-58 and 68-71 are withdrawn from consideration as being directed to non-elected inventions. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 51-55 and 59-67, in so far as they are directed to a method for screening of Alzheimer's disease by detecting API-6 in a biological sample, are under examination in the instant office action.

Specification

3. The disclosure is objected to because it contains a number of embedded hyperlinks and/or other form of browser-executable code (see pages 8, 24, 54 and Table X on page 98, for example). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The use of the trademarks has been noted in this application (see page 66, lines 12 and 26, page 124, lines 12 and 14, for example). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is advised to review the entire text of the instant specification for other possible use of trademarks or hyperlinks.

Claim Objections

4. Claim 59 is objected to because of the following informalities: "administer" (fourth line of the claim) should be "administered", perhaps. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 51-55 and 59-67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant invention (claims 51-55 and 59-67) is directed to methods for screening, diagnosis or prognosis of Alzheimer's disease (AD), for determining stage or severity of AD, for identifying subjects at risk of developing of AD and for monitoring the progress of a treatment of AD by detection of API-6 in a biological sample of a subject. The invention is based on the results of the study where using the protocol provided in WO 98/23950 document (Parekh et al, 1998) for identifying molecules in a biological sample and presenting the results in a computer-readable format, AFs (Alzheimer's Disease-Associated Features) were identified "by comparing

CSF samples from subjects having Alzheimer's disease against CSF samples from subjects free from Alzheimer's disease" (page 11, lines 26-28 of the instant specification). It has been discovered that some of the identified AFs are decreased in CSF of AD patients (see Table I, pages 12-14), while some AFs were increased in CSF of subjects having AD (see Table II, pages 16-17 of the instant specification). Specifically, AF-21, which corresponds to the elected API (Alzheimer's Disease-Associated Protein Isoform)-6, subsequent to SEQ ID NO; 36, 37, 38 and 39 (Table IV) is found to be 1.30 fold decreased in subjects having Alzheimer's disease (Table I, page 12). Therefore, it was proposed that the detection of API-6 in a biological sample of a subject will implement the claimed method for screening, diagnosis or prognosis of Alzheimer's disease (AD), as well as for determining stage or severity of AD, for identifying subjects at risk of developing of AD and for monitoring the progress of a treatment of AD. However, the instant specification is not found to be enabled for the claimed method because it provides` neither enough guidance for such method of treatment, nor working examples, thus, requiring undue experimentation on part of one skilled in the art to discover how to practice the claimed invention.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. In re Wands, 8 USPQ2d, 1400 (CAFC 1988).

The state of the prior art is such that there is no reference of record that would associate API-6, which is represented by SEQ ID NOs: 36-39 with Alzheimer's disease or with neurodegeneration in general. The instant specification fails to provide any evidence or sound scientific reasoning that would support a conclusion that the decrease in presence of polypeptides of SEQ ID NOs: 36-39 in a biological sample of a subject would have any association with Alzheimer's disease.

Note that although the claimed method is not limited to quantitative detection of API-6 in a CSF sample of a subject, with regard to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enablement of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest reasonable interpretation of the claimed method is that it allows to screen, diagnose, make prognosis of Alzheimer's disease, determine stage or severity of AD, identify risk of developing AD and monitor the effectiveness of a treatment for AD by detecting API-6 in a biological sample of a subject. However, it is clear from the results presented in Table I, page 12, that AF-21 (which corresponds to API-6) is only decreased in subjects with AD compare to normal subjects. Thus, one of ordinary skill in the art would not reasonably conclude that detection of API-6 in a biological sample of a subject would associate such subject with any disease.

Moreover, one of skill in the art would not consider the fact that API-6 is found to be decreased in SCF of subjects having AD to be a reasonable assertion that such decrease can be implemented in screening, diagnosing, making prognosis of Alzheimer's disease, determining

the stage or severity of AD, identifying risk of developing AD and monitoring the effectiveness of a treatment for AD because there is no scientific evidence, reasoning or guidance provided in the instant specification to support such assertion and, consequently, the claimed method.

The standard of an enabling disclosure is not the ability to make and test if the invention worked but one of the ability to make and use with a reasonable expectation of success. In the instant case, one of ordinary skill in the art readily recognizes that in order to practice the claimed method the instant specification must describe not only the protocol of two-dimensional electrophoresis and process of quantitation of selected API-6, but also provide important information on, for example, how to practice the claimed method on other biological samples; how to estimate what level of decrease of API-6 can be considered sufficient to be associated with AD; what amino acid sequences from SEQ ID NOs: 36-39 are critical for determination that API-6 is decreased; it is also not clear how to resolve a possible situation when only one API is decreased and other APIs are increased etc. None of this essential information is provided in the instant specification.

In view of the lack of teachings and unpredictability of the art set forth earlier, and also the total absence of the working examples, the instant specification is not found to be enabling for a method for screening, diagnosis or prognosis of Alzheimer's disease (AD), for determining stage or severity of AD, for identifying subjects at risk of developing of AD and for monitoring the progress of a treatment of AD by detection of API-6 in a biological sample of a subject. It would require undue experimentation and making a substantial inventive contribution for the skilled artisan to discover how to use Applicants' invention as currently claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 51-55 and 60-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 51 is vague and indefinite for recitation of "Accession No. 15179". If this recitation refers to a particular sequence, then the sequence must be identified by a sequence identifier in accordance with the sequence rules requirements of 37 C.F.R. § 1.821 through 1.825. If this recitation refers to the deposition of a biological material, such information must be clearly identified in the instant specification and the claims. Clarification is required.

8. Claim 63 is vague and ambiguous because it is not clear what "other members of the gene family" are encompassed by the claim.

9. Claims 52-55, 60-62 and 64-67 are indefinite for being dependent from indefinite claims.

Conclusion

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (703) 305-1003. The examiner can normally be reached on Monday to Friday 9 AM to 5 PM ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (703) 308-6564. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 782-9306 for regular communications and (703) 782-9307 for After Final communications.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556 or (703) 308-4242. If either of these numbers is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Olga N, Chernyshev, Ph.D.
November 25, 2002 OC

JOHN ULM
PRIMARY EXAMINER
GROUP 1800